UGT1A1: Focus on Irinotecan

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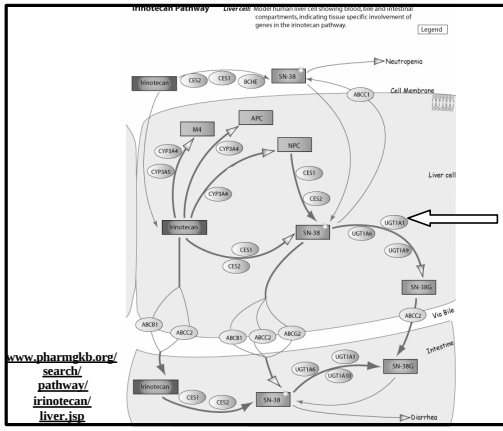
Conflict of Interest Disclosure (Relevant to Talk)

- **Co-inventor on several pending/issued patents related to UGT1A1 diagnostics**
- **Shareholder in Nuvelo (acquirer of Variagenics), which currently has rights to related pharmacogenetic IP**

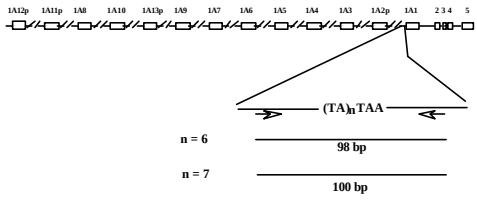
Irinotecan

- **Cytotoxic agent approved for metastatic colorectal cancer**
  - **Usually administered in combination with 5-FU**
  - **Also active in many other malignant diseases**
- **Usage limited by toxicity**
  - **Neutropenia**
    - **Primarily on q3 week schedule**
  - **Diarrhea**
    - **Primarily on weekly (4 on, 2 off) schedule**



www.pharmgkb.org/search/pathway/irinotecan/liver.jsp

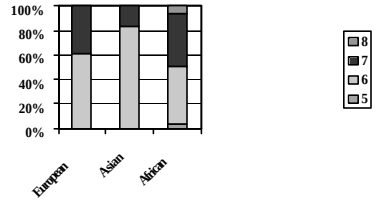
Variation (Indel) at the *UGT1A1* Promoter

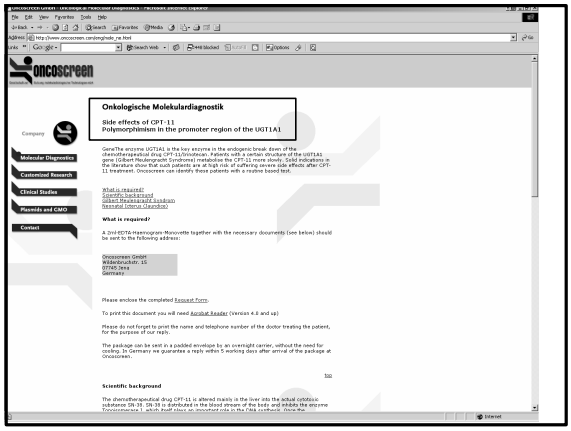


Bosma, NEJM, 1995
Monaghan, Lancet, 1996

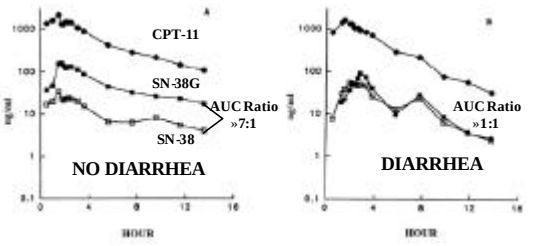
UGT1A1 Promoter Allele by Ethnic Group

Beutler, PNAS, 1998





Diarrhea (weekly schedule) is correlated with decreased glucuronidation of SN-38



Gupta, *Cancer Res*, 1994

MJR040902

Four Candidate Functional Polymorphisms in *UGT1A1* Exon 1

- Consistent evidence
  - TATA box indel (6/7) (**28*)
  - 211 G>A (G71R) (**6*)
- Unconfirmed evidence
  - -3156 G>A (in PBREM) (includes most **28*)
  - -3279 T>G (in PBREM) without **28* (**60*)

Adequately Sized Studies of *UGT1A1*28* and Irinotecan (SN-38)

- Iyer, Clin Pharmacol Ther, 1999
  - *In vitro* glucuronidation (44 microsomes)
    - 6/6>6/7>7/7
- Ando, Cancer Res, 2000
  - Case-control study of 118 Japanese (toxicity, allowed other drugs)
    - 7/7, 6/7>6/6
- Iyer, Pharmacogenom J, 2002
  - Prospective clinical study of 20 Americans (neutropenia and PK)
    - 6/6>6/7>7/7

Adequately Sized Studies of *UGT1A1*28* and Irinotecan (SN-38) (continued)

- Mathijssen, Clin Cancer Res, 2003
  - PK study of 65 Europeans
    - No significant correlation
- Font, Invest New Drugs, 2003
  - Clinical study of 51 Spaniards (with docetaxel)
    - No significant correlation
- Innocenti, J Clin Oncol, 2004
  - Prospective clinical study of 66 Americans (neutropenia and PK)
    - 6/6>6/7>7/7

Adequately Sized Studies of *UGT1A1*28* and Irinotecan (SN-38) (continued)

- Paoluzzi, J Clin Pharmacol, 2004
  - PK study of 94 Europeans
    - 6/6>6/7,7/7
- Sai, Clin Pharmacol Ther, 2004
  - PK study of 85 Japanese
  - 6/6>6/7>7/7
- Rouits, Clin Cancer Res, 2004
  - Clinical study of 75 Europeans (toxicity, with 5-FU)
    - 7/7>6/7>6/6
- Marcuello, Br J Cancer, 2004
  - Clinical study of 95 Spaniards (diarrhea, allowed other drugs)
    - 7/7>6/7>6/6

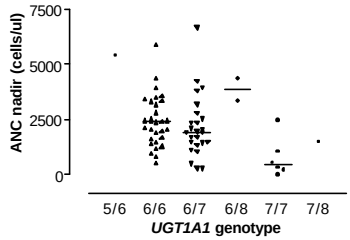
Irinotecan pharmacokinetics and TA indel genotype

	Irinotecan AUC (mg*h/ml)	SN-38 AUC (ng*h/ml)	SN-38G AUC (mg*h/ml)	Glucuronidation ratio
6/6 (n=30)	24.4±7.8	336±168	2.0±1.4	6.5±4.0
6/7 (n=25)	26.1±10.8	458±380	1.9±1.7	5.6±4.8
7/7 (n=6)	25.4±6.7	542±195	1.8±1.3	3.6±2.8

Nonparametric trend analysis, p=0.03

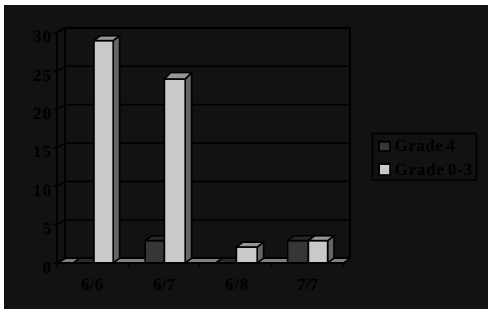
Neutropenia (q3 wk schedule) is Correlated with *UGT1A1* Genotype (*28)

(Innocenti et al, JCO, 2004)



Bar represents median values.
Nonparametric trend analysis among 6/6, 6/7, 7/7, p<0.01

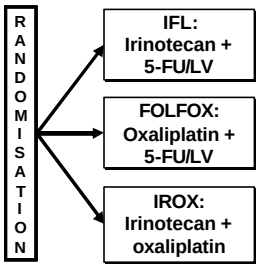
Grade 4 neutropenia and TA indel genotype



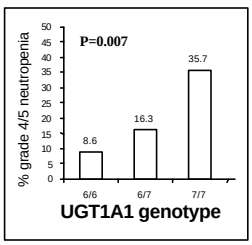
Fisher's exact test for 6/6, 6/7, 7/7, p=0.001

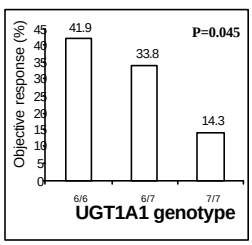
N9741: Schema (McLeod, ASCO, 2003)

524 stage IV patients



N9741 (NCCTG pharmacogenetic study)





N=524

Washington University School of Medicine
CREATE
Pharmacogenetics Research Network

*UGT1A1*6* (G71R)

- **Limited to Asian populations**
- **Expression studies demonstrate 30% of wild-type activity**
- **q of 0.15**
- **Consistently associated with neonatal hyperbilirubinemia in Asian populations**

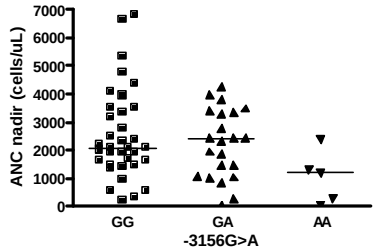
Adequately Sized Studies of *UGT1A1*6* and Irinotecan

- **Ando, Cancer Res, 2000**
  - **Case-control study of 118 Japanese (toxicity, allowed other drugs)**
    - **No significant correlation**
- **Sai, Clin Pharmacol Ther, 2004**
  - **PK study of 85 Japanese**
    - **Multiple regression suggested codominance, with effect 90% of that of **28***

Candidate *UGT1A1* PBREM variants

- **-3156 G>A**
  - **q of ~0.3 in European and African populations (Innocenti, Pharmacogenetics, 2002)**
  - **Lower q (0.13) in Asians (Sai , 2004)**
  - **A always associated with TA7**
    - **Within TA7 haplotypes, A:G ratio varies with ethnicity**
      - **European 6.2, African 3.3, Asian 25**
  - **Associated with neutropenia and PK in one study (Innocenti, 2004)**
    - **Had stronger association than TA7**

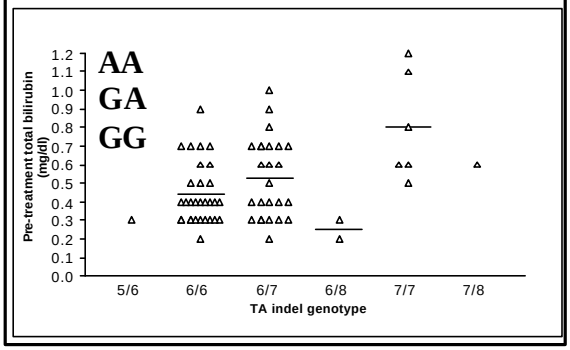
UGT1A1 PBREM SNP (-3156) was the Best Predictor of ANC Nadir



P=0.02

Innocenti et al, *J Clin Oncol* , 2004

Effect of TA indel and –3156G>A on total bilirubin



Candidate *UGT1A1* PBREM variants

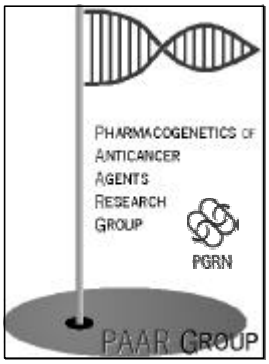
- **-3279 T>G**
  - **If TA6, then can be denoted as *UGT1A1*60***
    - **European 0.09, African 0.32, Asian 0.14**
  - **TA7 almost always associated with -3279G**
  - **In one study (Sai, 2004), associated with PK (and bilirubin) in univariate, but not multivariate analysis**
  - **In a 2nd study (Innocenti, 2004), no evidence for association with PK or toxicity**

My (Biased) Assessment of the Available Data

- ***UGT1A1*28* should be considered as a valid biomarker (distinguishing 3 genotypes) for decreased UGT1A1 activity**
  - **And for increased irinotecan toxicity**
- ***UGT1A1*6* should be considered as a valid biomarker (distinguishing 3 genotypes) for decreased UGT1A1 activity**
  - **Prospective studies of its association with irinotecan toxicity are indicated (in Asian populations)**

My (Biased) Assessment of the Available Data (continued)

- ***UGT1A1* -3156 G>A should be studied further to assess whether it is superior to **28* as a marker of UGT1A1 activity**
- ***UGT1A1*60* should be studied further, particularly in African populations where it has the highest frequency**



http://pharmacogenetics.org